Journal of Aging Science
ISSN: 2329-8847

Boccardi and Paolisso, Aging Sci 2013, 1:2
DOI: 10.4172/2329-8847.1000108

Short Communication Open Access

Malleability of Short Telomeres by Telomerase Activators: A Mini-review

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Most human cells lack sufficient telomerase to maintain telomeres; hence they shorten with each cellular division leading to organismal aging and disabling age-related diseases susceptibility. Genetic studies in mice demonstrated that short telomeres rather than average telomere length are associated with most age-related diseases and that rescue of short telomeres by telomerase is sufficient to restore cell and tissues viability. Novel findings in telomerase activation suggested its role as a new therapeutic strategy to prevent or at least retard cellular senescence and organismal decline, potentially impacting on human health.

Telomeres are specialized structures composed of tandem nucleotides repeats bounded by specific proteins at the end of eukaryotic chromosome which protect them from degradation and DNA repair activity [1]. Due to the "end replication problem" telomeres shorten with each cell division, representing a mitotic clock leading cell to become irreversible arrested – senescent [2,3]. Telomerase is a reverse transcriptase able to elongate telomeres during cell division and replication events, but silenced in most somatic cells immediately after birth, thus telomeres progressively shorten along with aging [4]. When telomeres reach a critically short length cannot be repaired and consequently trigger a persistent DNA damage response leading to cellular senescence and/or apoptosis [5]. The accumulation of senescent cells in the tissues and organism as whole can compromise tissue regenerative capacity and function contributing to organismal aging [5]. As an indicator of cellular senescence telomere length has been postulated as a biomarkers of human aging [6]. Evidences have accumulated during years for the association between telomere shortening and human health; in particular, accelerated telomere attrition has been implicated in many age-related disorders from progeroid syndromes over an increased risk of cancer to atherosclerosis, diabetes and even Alzheimer disease, strongly impacting on human health [7,8]. However genetic studies in mice have demonstrated that short telomeres rather than average telomere length are associated with age-related diseases and that rescue of short telomeres by telomerase is sufficient to restore cell and organismal viability and genomic stability [9,10]. Supporting this, both telomerase-deficient mice and human diseases due to mutations in telomerase components result in shorter telomeres, accelerated-aging phenotypes and decreased longevity due to premature depletion of stem cells and subsequent organ/tissue failure, suggesting that telomerase and consequent telomere shortening play a key and limiting role in tissue maintenance during organismal lifespan [11-13]. Telomerase constitutive activation by using transgenic mouse in adult tissues has pinpointed a role for telomerase in tissue fitness and prevention of aging, resulting in an improved extension of lifespan [14-16]. Most importantly, activating telomerase later in life, mice showed a healthier phenotype compared to their control littermates and displayed a reduction in most disabling conditions associated with physiological aging such as osteoporosis and insulin resistance, while physical performances, metabolic functions and cognitive skills were significantly improved [14,17]. These changes were associated with an overall increase in telomere length as well as a reduction of short and very short telomeres [14,17,18] suggesting that telomerase activation may play an important role in tissue regeneration of adult organisms and may represent a proof-of-principle that aging can be retarded even in humans.

The first potential telomerase activator described is the small molecule TA-65, derived from an extract of a plant commonly used in traditional Chinese medicine, *Astragalus membranaceous*. TA-65 dietary supplementation in female mice is capable of increasing telomerase levels in some mouse tissues and elongating critically short telomeres, leading to an improvement of certain health-span indicators including osteoporosis, skin fitness and glucose tolerance, without significantly increasing the global cancer incidence [19,20].

The use of TA-65 as a treatment to improve health-span in humans has been tested in past few years, where volunteer subjects took part in an open label comprehensive dietary supplementation program, which included a TA-65 dose of 10-50 mg daily [21]. Report analysis of the first treatment year has been recently released, demonstrating high tolerability and beneficial effects in humans [21]. TA-65 is able to upregulate basal telomerase activity levels in neonatal human keratinocytes, leading to a decline of senescent and natural killer cells together with a significant reduction of the percentage of cells with short telomeres. Again, very recently it has been shown that in addition to apparent positive immune remodeling, TA-65 may improve markers of metabolic, bone and cardiovascular health [22].

Recently it has been shown that telomerase activity is also responsive to lifestyle and mindset, representing a natural way to stimulate telomerase activity [23-26]. With intensive lifestyle modification, including a low fat diet, increased activity and stress reduction, telomerase activity increases significantly in peripheral blood mononuclear cell over 3 months, suggesting that it is capable of immediate and short term changes. Most importantly, it has been shown that subjects highly adhering to Mediterranean diet have higher circulating telomerase activity, showing a better healthy status [27]. Indeed another study showed that statins may represent a novel telomerase activator since subjects on statin therapy have higher circulating telomerase activity levels and longer telomeres compared the control group and an increasing in telomerase activity along with age was also described [28]. These results, according to previous results *in vitro*, suggest that human telomerase may have primarily a telomere-stabilizing function that allows cells to proliferate by protecting telomeres when they remain critically short. Hence, rescue and selective expansion of near-senescent cells with short telomeres could lead to a reduction in the population mean telomere length. Thus, telomerase activation with chemical or natural activators, such as

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Received August 24, 2013; **Accepted** September 03, 2013; **Published** September 08, 2013

Citation: Boccardi V, Paolisso G (2013) Malleability of Short Telomeres by Telomerase Activators: A Mini-review. Aging Sci 1: 108. doi: 10.4172/2329-8847.1000108

specific diets, may lead to longer life expectancy and successful aging; however evidences are still poor and further studies are necessary to clarify such an association.

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